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The effect of reduction on the rotatory power of some furan compounds

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THE EFFECT OF REDUCTION ON THE ROTATORY POWER OF SOME FURAN COMPOUNDS

by

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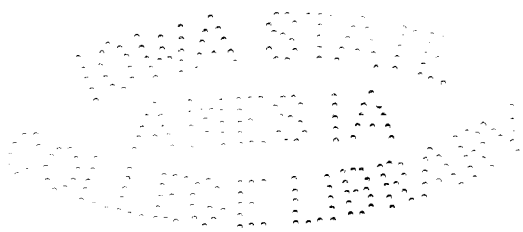

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INTRODUCTION

The phenomenon of optical activity has been investigated by chemists from the time of its discovery by Biot in 1812. Two very important advances have resulted from this study, the proposal of the "molecular dissymmetry" theory by Pasteur in 1848, and the postulation of a tetrahedral structure for the carbon atom by Le Bel and van't Hoff in 1874. These principles are the foundation of modern stereochemistry and serve as a basis for the prediction of all possible active types. They do not, however, give any indication of the structural feature that is responsible. Work to this end has resulted in the accumulation of a great mass of data. Much of this has been of little value in the solution of the problem because many of the variables involved in any one measurement have not been fully understood.

Within recent years physicists have established the theoretical basis for optical activity and have derived rotatory dispersion equations. These are, however, of little use to the chemist because they cannot be applied to simple molecules that are most easily handled experimentally, neither are they expressed in terms of easily measurable properties.

Optical rotatory power has been used as a means of determining the structure of organic compounds; such as, whether or not double bonds are conjugated. It has also been suggested

as a means of estimating dissociation constants of acids and phenols where these are not easily obtainable by other methods. These uses are of limited value with our present understanding of rotatory power, and they are not justified at all unless the optical properties of a number of closely related compounds are studied first. The main contribution of a solution of this problem will probably be in the determination of the finer structure of organic molecules and its possible correlation with the mechanism of reactions. The failure of physical methods to develop a workable formula seems to justify continued chemical investigation.

HISTORICAL

A considerable part of the work on optical activity since the time of Le Bel and van't Hoff has been done in an attempt to correlate the optical rotatory power of compounds with their chemical constitutions. While most of the results have been expressed in rather broad generalizations, an early attempt was made to place the relationship on a quantitative basis. In the case of the optical activity of a molecule with one asymmetric carbon atom, Brown (1) reasoned that there must be a function k for each radical attached to the asymmetric carbon atom which could be expressed numerically depending on its composition, constitution, and the temperature of the substance. Since the rotation becomes zero when any two k's are equal, it must depend on a product of the differences. This principle has become known as the "product of asymmetry" and may be expressed as

$$\alpha = \frac{(a-b)(a-c)(a-d)(b-c)(b-d)(b-c)}{(a+b+c+d)}$$

where a, b, c, and d represent the values of k for the radicals. If any two groups are interchanged it is evident that an odd number of the differences change sign, and the sign of the rotation is changed although remaining the same in magnitude. This condition, of course, exists in the case of two enantiomorphic forms. Brown pointed out that it should be de-

termined if possible whether this function k of a radical were a constant, or whether it varied, depending on what other radicals were present in the molecule. He did not suggest how this value of k could be established but indicated that it could not be derived from the mass of the radical.

Previous to the paper by Brown, Guye (2) had proposed the same theory, but he considered the mass and distance of a radical from the asymmetric carbon atom the determining factors in its effect on the rotatory power. In order to test this theory Walden (3) esterified active malic acid in such a way as to place two radicals of equal masses on the asymmetric carbon atom. He found that such isomeric compounds had rather high rotatory power, thus showing that mass was not the controlling factor. Soon so many such discrepancies were reported that Guye (4) was forced to state that it was not the mass but rather the relative positions, the actions on each other, the "configuration", and, finally, the nature of the elements themselves that determined the direction and extent of the rotation.

One of the most striking illustrations of the failure of the mass to express a group's effect on the rotatory power was soon brought out by the preparation of similiar compounds containing isomeric alkyl groups. The great differences in the effects of these groups cannot be explained by any of the modern theories. In comparing the rotations of n-propyl and isopropyl secondary carbinols, Marshall (5) considered that

the higher polarity of the isopropyl group may explain the much greater effect it has on rotatory power. Stevens (6), however, pointed out that the difference in polarity as measured by acid dissociation constants cannot explain it, because the constants for butyric and isobutyric are very nearly the same. Kuhn and Freudenberg (7) believe that the difference in the absorption bands in the ultra-violet may account for the effect.

The difference in the effect of the isomeric alkyl groups has done much to discredit the product-of-asymmetry theory, but here the principle itself is really not involved and has never been disproved. A few investigators have attempted to solve some of the problems suggested by Brown. Bose and Willers (8) examined the observed rotations of forty-two compounds having seventeen radicals in common, and, by a series of approximations, assigned arbitrary constants to the different groups. They then calculated the rotations for the series of compounds and compared them with the observed values. While many showed fair agreement, others varied as much as fifty percent. Walker, Smiles, and Dover (9) used the same procedure with a series of esters of lactic and succinic acids. They found much closer agreement between the calculated and observed values for most of their compounds than had Bose and Willers, but some of theirs also varied as much as fifty percent.

Although these investigators did not consider their work to be conclusive, their results certainly do not indicate that

a radical has the same effect in different compounds. However, experimental difficulties might well account for the discrepancies found. For instance, all observed rotations were measured in the homogeneous state. Since many of the compounds used contained hydroxyl and ester groups, they were undoubtedly associated. Recent work on the effect of solvents has shown that rotations in a non-associating solvent more nearly express the true rotatory power of such compounds. In addition to this the esters of lactic acid are very difficult to prepare, and successive preparations by Walker and his associates did not have the same rotatory power, which fact suggests that they may have been working with optically impure compounds. These errors, even though small, could easily lead to rather large deviations when used in a product of differences. The difficulties that arise in the preparation of any large group of optically pure compounds have discouraged further attempts to solve the problem of group constants by the chemical method.

All of the modern theories of optical activity have been developed on the physical basis. The foundation for this method of attack was laid by Fresnel (10) when he interpreted the rotation of a wave of plane polarized light as circular double refraction. He considered plane polarized light as being made up of two superimposed waves of circularly polarized light of opposite sense and equal in amplitude. If the two waves have different velocities in a medium, that is, if the medium

exhibits circular double refraction, the plane of polarization is rotated and in the sense of the component having the greater velocity. Similiar to this phenomenon is the differential absorption of right and left circularly polarized waves, causing circular dichroism. This causes the phase relationship to change so that the emergent ray is no longer plane polarized but is elliptically polarized. This occurs near the wave length of an optically active absorption band and causes an inflection in the rotatory dispersion curve. Cotton (11) found that if the band furnished the main contribution to the rotation an inversion of the rotatory dispersion curve took place at the wave length of maximum ellipticity, which is approximately the region of maximum absorption. These relationships are known as the Cotton Effect.

Drude (12) contributed much to the development of the theory of optical rotatory power by deriving the first accurate rotatory dispersion formulae. The simple form, which applies only to regions of complete transparency, is $\alpha = \frac{k}{\lambda^2 - \lambda_0^2}$, k being the rotation constant and λ_0 the dispersion constant. These constants k and λ_0 are characteristic of the substance. The values of λ are usually expressed in microns.

Theoretically λ_0 corresponds to a fundamental vibrational frequency of the molecule and is approximately the wave length of the center of an active absorption band. Tschugaeff was the first to recognize the importance of the absorption regions of

a molecule on its rotatory power. The critical frequencies for most compounds lie in the ultra-violet or visible part of the spectrum. These compounds also have infra-red absorption spectra, but Condon (13) reported that the rotations of several compounds have been measured out to 2.14 microns and there were no detectable irregularities. This indicates that these absorption bands contribute nothing to the rotatory power. Wood and Nicholas (14) also made quantitative measurements on methyl and ethyl tartrate derivatives and could find no justification for adding an infra-red term to the dispersion equation.

Lowry and Dickson (15) pointed out that the constant k in Drude's equation is a measure of the molecular asymmetry since it is not dependent on the dispersion. Thus when $\lambda=\sqrt{\lambda_0^2+1}$, the rotation will be equal to k, which they called the absolute rotatory power. They suggested that comparisons of the rotatory power of different compounds would be valid only when made at such a wave length. Little use has been made of this relationship except by Betti (16).

Lowry found that while the dispersion of most organic compounds could be expressed by one Drude term, many required two or more terms. Such compounds were said to have complex rotatory dispersion. Theoretically there should be as many terms as there are active absorption bands in the molecule. In the case of simple rotatory dispersion, terms after the first are probably small and cancel each other exactly. It is very difficult to determine experimentally the constants for

any but the main contributions; therefore, where the dispersion is complex the latter terms may be a sort of average of several contributions. In this case λ_0 will have no physical significance, especially if there are a number of active absorption bands in the same general region of the spectrum.

Some complex dispersion curves exhibit anomalies, that is, pass through a maximum and then change sign at shorter wave lengths. Tschugaeff (17) was the first to distinguish clearly between the different types of anomalous dispersion. This phenomenon may be caused by: a mixture of two kinds of active molecules, the presence of an optically active absorption band, the superposition of two active centers in the same molecule, or the presence of two partial rotations arising from groups attached to the same asymmetric carbon atom. In the cases where two rotations are involved, they must be of opposite sign and unequal dispersion to produce an anomaly.

There is little question from the physical standpoint about the general theory of optical rotatory power. The rotation is believed to arise from the same oscillators that produce refraction. By applying the electromagnetic theory of light to a set of harmonic oscillators the existence of circular double refraction can be demonstrated. This method has been used by a number of investigators who obtained analogous dispersion equations. By means of a quantum mechanical treatment Rosenfeld (18) derived equations which Condon (13) proved were equivalent to those derived by the classical

method. In order to find a practical dispersion formula it is necessary to choose the resonator model in such a way that its shape and constants can be expressed in terms of known properties of molecules. Few of the formulae that have been developed have been stated in terms that can be applied to even the simplest compounds. Born's (19) original formula was used by Hylleraas (20) to calculate some of the optical properties of quartz crystals, and he found excellent agreement with the experimental values. More complex systems like those encountered in organic molecules in the liquid state cannot be treated by this formula.

Kuhn (21) found the simplest oscillating system that would give rise to optical activity to be two coupled harmonic oscillators vibrating at right angles to each other. His model cannot be applied to a molecule with an asymmetric carbon atom, but only to spiro-type compounds having two rings at right angles to each other. This has limited the practical application of his theories, but his equations relating circular dichroism to optical rotatory power within an absorption band have been responsible for much of the recent progress in the understanding of optical activity, expecially in the study of partial rotations.

Born (22) has recently revised his theory in order to develope an equation that would relate optical activity to some known properties of the molecule. His latest model, like Kuhn's, corresponds to a spiro-type compound but is applicable

only in regions of complete transparency.

It has been pointed out that the rotation of a molecule is the sum of the contributions of its absorption bands, that is: $\alpha = \sum \frac{a_i \lambda_i^2}{\lambda^2 - \lambda_i^2}$. According to the accepted theory, oscillators in a molecule must be coupled before they become optically active. From his mathematical treatment, Kuhn found that if λ_1, and λ_2 are coupled, $a_1 = -a_2$. It follows from this, that, taken over the spectrum as a whole, $\sum a_i = 0$. Furthermore, the rotatory power becomes zero at both ends of the spectrum; since, at the longer wave lengths, the value of each Drude term approaches zero, and at the shorter wave lengths, the value of each term approaches a_i, the sum of the a_i terms being zero.

Kuhn has shown that the ratio of the rotational contribution of a band to the strength of a band is a constant throughout the spectrum which he called the anisotropic factor g. The rotational contribution of a band is its contribution to circular double refraction and the strength of a band is its contribution to ordinary refraction. Formulae for calculating g have been derived, but little data for testing them are available, because sufficient dispersion measurements are seldom made. However, Hunter (23) determined the dispersion and rotatory dispersion of d-secondary octyl alcohol over a wide enough range so that he was able to derive accurate empirical formulae for its refractive index and rotatory power. From these formulae Condon (13) determined the effective rotational strength of the group of bands having an effective wave length

of 1700A. From this he calculated the anisotropic factor to be $1.35X10^{-5}$ which he considered typical for strong absorption bands. Weak absorption bands may have much higher values for g.

The refractivity of a compound is a sum of the contributions of the absorption bands present, all positive quantities, whereas the rotatory power is a sum of positive and negative contributions. For this reason Born and others reject theories such as those of Boys (24) and de Malleman (25) where the rotatory power is expressed in terms of the refractivity of the groups attached to the asymmetric carbon atom. Such theories also do not account for the fact that in many cases weak absorption bands furnish the main contributions to the rotatory power.

Kuhn has found out a great deal about the effect of absorption bands on rotatory power by studying partial rotations in regions of absorption. For instance, the dimethyl amide of α-azidopropionic acid shows a band at about 2900A. This can be definitely assigned to the azido group since it appears whenever the group is present in a compound and vanishes when the group is eliminated. The rotatory dispersion curve of an ether solution of this compound has an inflection at about 2900A, showing that the band is active. Using the observed rotatory dispersion data, the half width of the absorption band, and choosing a value for a_i, Kuhn was able to calculate the partial rotation curve for this band. When this curve was

subtracted from that of the compound, the partial rotation curve for the rest of the molecule was obtained. This showed simple dispersion, i. e., increasing rotations with decreasing wave lengths with no irregularities near 2900A. This indicated that Kuhn's method of treatment was correct.

A comparison of the partial rotation curves shows that the N_3 band contributes about twenty percent of the total rotation in the visible. Since it furnishes only 1/100,000th of the total absorption, it must be comparatively very active. This is shown also by the value for g which has been calculated to be 2×10^{-8}. The partial rotation arising from this band is not the only contribution of the azido group to the rotation of the compound. The group has other strong absorption bands further in the ultra-violet. These may also have anisotropic factors and contribute something to the rotation in the visible.

The total effect of an absorption band on the rotation of a molecule may be considered, according to Kuhn, as being the result of two actions. The band brings into the molecule an inactive anisotropy which may become active by coupling with some other band. If it does couple, becoming anisotropic, this is called induced "anisotropy", and it induces anisotropy in the band with which it couples through its "vicinal action". Whether or not coupling will occur between two bands cannot be predicted, but from Kuhn's theoretical considerations it is evident that the coupling is at a maximum when the vibrating moments corresponding to the absorption bands are oriented at

90°, while the anisotropic factor is maximum when the vibrators are nearly anti-parallel. The distance is also important, but the limiting values are not known.

The functioning of the induced anisotropy and vicinal action of individual absorption bands has been illustrated by Kuhn (26) by means of the dimethylamide and methylester of azidopropionic acid. The compounds were configurationally related since they were prepared from the same active acid chloride, a reaction that permits no Walden inversion. The rotation of the ester was found to be weakly positive, whereas that of the amide was strongly negative. Comparison of the partial rotations showed that the contribution of the azido group was the same in both compounds; that is, its induced anisotropy was the same in both cases. In the case of the ester, the sign of the anisotropy of the group is determined by the arrangement of the H, CH_3, and $COOCH_3$ groups, while its magnitude is determined by their combined vicinal actions. In the same way the H, CH_3, and $CON(CH_3)_2$ groups determine the induced anisotropy of the azido group in the amide. Changing $COOCH_3$ to $CON(CH_3)_2$, therefore, has very little effect. The examination of many similiar cases lead Kuhn to believe that the induced anisotropy of a group is relatively little affected by chemical changes in the neighboring groups. This means that Brown's function k is approximately a constant for each group regardless of where the group appears.

The remainder of the rotations of the above molecules is

apparently due to the partial rotations of the $COOCH_3$ and $CON(CH_3)_2$ groups since the carboxyl absorption band is next strongest to that of the azido group. The induced anisotropy of each group is the result of the vicinal action of the same groups; namely, H, CH_3, and N_3. Kuhn found, however, that the partial contributions were the reverse of each other, $COOCH_3$ being positive and $CON(CH_3)_2$ negative. Thus, the induced anisotropy of a substituent is very sensitive to chemical changes within it even when the resulting group is of similiar chemical character. Such changes need not be drastic enough to shift the characteristic frequency of the band; for, ecording to the accepted theory, small variations in the distance or orientation of coupled vibrators may be sufficient to cause profound changes in rotatory behavior.

This sensitivity of the electron vibrator to its eviron-ment serves as a convenient method of explaining the marked effect of solvent and temperature on rotatory power. Compounds having complex rotatory dispersion are much more sensitive to changes in these conditions. In such cases a change in temperature or solvent undoubtedly has opposite effects on the Drude terms expressing the dispersion; thus, relatively large changes in the total rotation might occur, and a change in sign could take place if the terms were of the same magnitude. Earlier theories attempted to explain such variations on the basis of the association of the solute or of the solute and solvent. These reactions undoubtedly have some effect for

Rule (27) has found that the rotation of a compound in a series of solvents decreases with increasing polarity of the solvent. It has been observed that in many cases decreasing the concentration of a polar solute in a non-polar solvent causes an increase in the specific rotation. At least part of this effect is due to the decrease in the polarity of the medium and the reduction of the association between the solute molecules. For this reason, rotations of polar liquids in non-polar solvents are considered to more nearly represent the true rotatory power than rotations taken on the pure liquids. Association is not always accompanied by a decrease in rotation, for Walden (28) found that the diamyl ester of itaconic acid changed from a mobile liquid to a hard, colorless glass due to polymerization, but the rotation through these changes remained practically constant. Freundler (29) also found that, on changing solvents, tetra-substituted tartaric acid esters increased in rotation as association increased, association being measured cryoscopically. These results indicate that Rule was fortunate in his choice of active compounds in order to obtain such a regular change in rotation with polarity.

The temperature effect is also variable, as Pickard and Kenyon (30) found in a long series of systematic investigations in which they measured the rotations of many compounds from room temperature up to their boiling points. The change was rather small, showing a regular increase or decrease with increasing temperature. They worked with pure compounds and

attributed the change to dissociation; they believed the rotation at the boiling point represented that of the completely dissociated liquid. Still another source of variation due to temperature may arise in compounds having restricted free rotation. Wolf (31) found that at room temperature there is no free rotation of the halves of tartaric acid ester. He found three probable positions of minimum potential energy in which the molecule may become stationary; an increase in temperature would lead to a gradual perfection of free rotation with a resulting change in rotatory power. Further understanding of the effects of solvent, temperature, and concentration on rotatory power await the experimental determination of their effects on partial rotations.

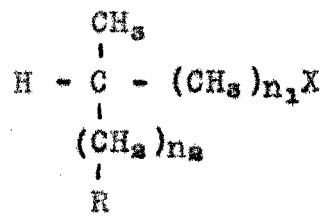
Some of the most interesting results from the study of optical activity have come from the investigation of homologous series. Many years ago Frankland predicted that anomalies in physical properties might appear in such series at the fifth carbon in a normal alkyl chain, since, when properly oriented, the hydrocarbon chain could form a complete spiral at this point. In their earlier work on homologous series, Pickard and Kenyon found that the rotatory power tended to vary regularly with increasing molecular weight. However, when the rotations of the methyl-n-alkylcarbinols were plotted against the molecular weight, the propyl member was found to be abnormally high. In many other series (32) also, such irregularities usually occurred when an unbranched chain of carbon or carbon and oxygen

atoms contained five, or a multiple of five, members. These irregularities were intensified at high temperatures and in solvents. In series containing ester groups or branched chains, more irregularities occurred, but these could always be explained as arising from the formation of some such spiral.

These abnormalities may be interpreted as being the result of a space effect. The existence of such an effect has been further confirmed by Lowry (33). He measured the optical properties of the acetates of the open chain aldehydic μ-forms of glucose, galactose, and arabinose prepared by Wolfrom. From the absorption spectrum and rotatory dispersion, Lowry found that the total rotations of these compounds were made up of an l-rotation, due to the induced dissymmetry of the aldehyde group, and a fixed d-rotation, due to the rest of the molecule. The partial rotation of the aldehyde group is more than doubled by the change in configuration of the fourth carbon in going from the glucose derivative to that of galactose, and this rotation is decreased by one-fourth in the elimination of the asymmetry of the fifth carbon on passing from the galactose derivative to that of arabinose. In comparing these results with those obtained from cyclic sugars, Lowry found that the effects were much greater than one would expect for changes in the configuration of relatively distant carbon atoms. He concluded that the dissymmetric field of the asymmetric carbons must act directly across space instead of through the carbon chain, and that the aldehyde group must be oriented in such a way that it

is nearer to the fourth and fifth carbons than one would expect from the straight chain formula.

The most extensive study of rotatory power in homologous series has been conducted by Levene (34). He and his associates have prepared many series of configurationally related compounds of the general formula:



where X is a chromophoric group, and R may be a methyl or chromophoric group. By varying n_1 he was able to show how the rotatory power changes with the distance of the chromophoric group from the asymmetric carbon atom. When n_1 equals four, the effect of such groups is usually reduced to that of an alkyl group. In a number of such series he observed an "alternating induced polarity" effect that caused alternate members to have abnormally high rotations.

As has been indicated, the most difficult problem in the correlation of rotatory power with chemical constitution is that of finding some easily measurable property of a group that can be used to express its relative effect on rotatory power. The mass of a group has been shown to be irrelevant, except, as noted by Levene (35), in the case of normal alkyl groups. Several investigators have used the refractivity of a group to express its effect on this property, but the two phenomena are

fundamentally different in some respects, and there is considerable question as to whether such a method is justified. Boys (24) used the effective radii of the groups in his calculation of optical rotation, but this has not been generally accepted. The electronegativity of a group has been compared with its effect on rotatory power in a number of series of compounds. Good correlation has been obtained, but the use of this property is limited because it cannot be expressed exactly. The relative electronegativity of a series of radicals may be determined from specific inductivity capacities, or from the dissociation constants of acids, amines, or phenols. The different methods do not always give the same order of the radicals, but there is general agreement between them.

Betti (16) condensed active β-naphthol phenylaminomethane with a large number of substituted benzaldehydes to give compounds of the type: $CH_3-\underset{C_{10}H_6(OH)}{\overset{H}{\overset{|}{C}}}-N=\overset{H}{\overset{|}{C}}-R$. He found that the molecular rotation varied with the dissociation constant of the acid RCOOH.

Rule (36) prepared a number of l-menthyl and l-octyl esters of monosubstituted acetic acids and found that the rotations increased with the electronegativity of the radical substituted in the acid.

Levene (37) has studied the effect of polarity on rotatory power in a simpler series of compounds. He prepared a number of active α-n-alkylpropionic acids and, by a series of reactions, varied the polarity of the carboxyl group. He found

that in each series, the polarity of the radical and the rotation of the compound decreased in the order: $C{\equiv}N$, $COOC_2H_5$, $COOH$, $CONH_2$, $COCl$, CH_2SO_3H, CH_2X, CH_2SH, CH_2OH, CH_2NH_2. He believed that, in the light of the newer theories, such a relation existed only in the aliphatic series. If another polar group were introduced, its effect could not be predicted.

Another correlation between electronegativity and rotatory power has recently been observed by Pigman and Isbell (38) who prepared a large number of β-d-glucosides. They found that, with one exception, the molecular rotation increased with the electronegativity of the aromatic aglucon as measured by its dissociation constant. The smaller rotations of the aliphatic β-d-glucosides and β-d-glucose also showed a qualitative relationship to electronegativity, since the dissociation constants of alcohols and water and considerably smaller than those of the phenols. Pigman and Isbell justified the use of these compounds for this comparison by showing that the molecular rotation varied with the rotatory contribution of the first carbon, so the effect is as if the molecule had only one asymmetric carbon.

It is generally agreed that theoretically there should be a definite relationship between polarity and optical rotatory power, but the relationship may not be as simple as the above results indicate. It is claimed that the orientation in space as well as the polarity should be considered. Furthermore, if a chromophoric group is introduced into a molecule, the ab-

sorption bands present may affect its rotatory contribution to such an extent that the polarity effect is negligible.

Many investigators have attempted to explain the chemical and physical properties of organic molecules in terms of the electronegativity of the radicals present. Hixon and Johns (39) have arranged organic radicals in the order of their electronegativities using an arbitrary scale of units termed the electron-sharing abilities (abbr. E. S. A.). The order of the radicals is determined by the dissociation constants of the corresponding acids, and it has been shown that the same order exists if the radicals are placed by the dissociation constants of the amines. This property has been correlated with the chemical and physical properties of a number of series of compounds.

Burch (40) examined the rotations of some alpha-substituted ethylamines and Bulbrook (41) the rotations of some alpha-substituted pyrrolidines. In each series a qualitative relationship was found between the E. S. A. of the radical substituted and the rotatory power of the resulting compound. Naps and Johns (42) measured the rotations of a number of substituted succinic acids and the compounds obtained by ring closure of a number of their derivatives. With these compounds the effects were too complex to correlate the rotatory power with the E. S. A.'s of the groups present.

STATEMENT OF THE PROBLEM

Assuming that the optical rotatory power of a molecule having one asymmetric carbon atom depends on the radicals present according to the principal of the product-of-asymmetry, and, assuming that the group constants may be derived from their electron-sharing abilities, it is apparent that if the radicals have widely separated E. S. A.'s and the highest is capable of being varied throughout the entire range with retention of configuration, the rotation of the molecule will change in the following manner: It will decrease to zero as the E. S. A. of the varied group approaches that of the next highest group, then change sign, increase through a maximum, and decrease to zero as it approaches that of the next group, etc.

Many such cases of inversion of sign with retention of configuration have been reported in the literature, especially in a number of Levene's homologous series. However, these isolated cases, involving groups of limited range of E. S. A., do not provide enough data for an adaquate test of the theory.

The experimental procedure involved in changing the electronegativity of a group over a wide range becomes very difficult because such groups are not readily available. The furyl group can be changed in a limited number of steps over a wide range of E. S. A. It is relatively electronegative, the tetrahydrofuryl group is less electronegative, and the n-butyl

group is relatively electropositive. Such a series, of course, will not show the result of a gradual change in E. S. A., but may show two inversions of sign if the other groups are properly chosen. One of the groups must allow resolution of the inactive compound; the carboxyl group is suitable for this purpose.

Alpha-substituted acids are not satisfactory compounds for this study for several reasons. First, these acids, if they possess a hydrogen atom on the alpha carbon (asymmetric), undergo racemization easily during many of their reactions. Second, the carboxyl group is strongly influenced by solvent and temperature; consequently, if it is directly attached to the asymmetric carbon atom these influences will markedly affect the rotatory power of the compounds. Third, these acids offer many synthetic difficulties. For these reasons, a series of beta-substituted acids was chosen. A few of these acids have been reported, and Levene has prepared a number of configurationally related β-n-butyl acids such as would be obtained from such a series on complete reduction of the furyl group.

This series has a number of limitations. The most serious from the experimental side is that catalytic hydrogenation of the furyl group in an active molecule may introduce a second active center through asymmetric addition of hydrogen under the influence of the first active carbon atom. This means that an optically pure compound must be used for the hydrogenation and the product completely resolved so that the rotation of the compound with an inactive tetrahydrofuryl group can be calculated.

If this is not possible, the sign of rotation of the first active carbon will be in doubt. The second difficulty is that there is a hydrogen on the asymmetric carbon. Bose and Walker in assigning arbitrary constants to the various groups for the calculation of rotatory power gave hydrogen a rather high value. Those who believe that the effect of a group depends entirely on its absorption bands apparently assume that hydrogen has very little effect. On the other hand, if its effect depends on its electronegativity, hydrogen should be intermediate between the electropositive alkyl groups and the more electronegative groups. In view of this uncertainty the problem would be simplified if compounds could be studied that contained a tetra-substituted asymmetric carbon atom. Synthetic difficulties prevent this in the proposed series. In spite of this limitation it was felt that preliminary to a more exhaustive investigation of the connection between electronegativity and the product-of-asymmetry, the preparation of such a series of compounds would be helpful.

After a consideration of all of the above factors, it was proposed to pursue the following study; first, to prepare and resolve β-(α-furyl)-β-phenylpropionic acid, β-(α-furyl)-valeric acid, and β-(α-furyl)-caproic acid; second, to hydrogenate the furyl group in each compound to the tetrahydrofuryl group; third, to remove the oxygen from the ring, changing the tetrahydrofuryl group to the n-butyl group; and, fourth, to measure the rotatory power and dispersion of each of the above

compounds and to compare the signs of the rotations with what one would expect if the product-of-asymmetry theory is valid when the E. S. A.'s of the groups are used as their rotation constants.

EXPERIMENTAL

Preparation and Resolution of β-Substituted Propionic Acids

Preparation of β-(α-furyl)-valeric acid

The diethyl furfurylidenemalonate used in these preparations was made by a modification of Marckwald's (43) method. Ninety-six grams (one mole) of furfural were condensed with 160 grams (one mole) of diethyl malonate by means of 153 grams (1.5 moles) of acetic anhydride. The mixture was heated in a bath under a 15 inch fractionating column for 14 hours. The bath temperature was held at 135° during the first six hours which caused gentle refluxing. The temperature was gradually raised to 175° during the last eight hours. Slightly more than the theoretical amount of acetic acid distilled over during the latter heating period. Portions of the resulting thick, black liquid were transfered to a Claisen flask and distilled under reduced pressure. Practically all of the lower boiling fraction was acetic anhydride; a total of 35 grams was collected. The product distilled over at 165-170°/10mm. and amounted to 212 grams (0.89 moles), 89 percent of the theoretical. Another similiar run resulted in a 87.5 percent yield. The ester, a pale yellow, viscous liquid, gradually turned a very dark

reddish-brown color after standing for several months. This did not appreciably affect its reactivity.

A Grignard reagent was prepared in the usual manner from 9.0 grams (0.37 moles) of magnesium and 46 grams (0.42 moles) of ethyl bromide. The ether solution was cooled and a dry ether solution of diethyl furfurylidenemalonate was added slowly with the temperature kept below 10°. The reaction mixture was refluxed four hours, allowed to stand overnight, and then hydrolyzed with 10 percent acetic acid. The ether layer was separated and the water layer thoroughly extracted with several portions of ether. The combined ether extracts were shaken with sodium bicarbonate solution and then dried over anhydrous sodium sulphate. The ether was removed from the dried solution on a water bath, and the residue was fractionally distilled under reduced pressure. The product distilled at 136-140°/5mm. and amounted to 74 grams which is 78.8 percent of the theoretical based on the weight of ester used. Other smaller runs yielded 73 and 79.5 percent of the theoretical.

One hundred and ten grams (0.41 moles) of the substituted malonic ester were added to a 35 percent solution of 46 grams (0.82 moles) of potassium hydroxide. The mixture was refluxed two hours, 30 grams of a 50 percent solution of potassium hydroxide were added, and the refluxing was continued for one hour. Portions of the ester hydrolyzed less drastically contained some of the mono-ester which, after decarboxylation,

could not be separated from the β-(α-furyl)-valeric acid by distillation. The solution of the hydrolyzed ester was diluted with an equal volume of water, and this amount of liquid was then distilled off to remove the alcohol. The residue was cooled, made acid to Congo red, and extracted thoroughly with ether. The solution of the dibasic acid was dried over anhydrous sodium sulphate, the ether distilled off, and the acid decarboxylated by heating slowly to 190°. The residue was distilled yielding 58 grams of β-(α-furyl)-valeric acid (b.p. 113-119°/3mm.) which is 85 percent of the theoretical; n_D^{25} 1.4760; d_4^{25} 1.088.

Maxim and Zugravescu (44) prepared this acid by hydrolysis of its diphenylamide. They reported a boiling point of 145°/17mm.

Resolution of β-(α-furyl)-valeric acid

Although no general rules can be applied, mono-basic acids have been most easily resolved by means of quinine. Levene used quinine and cinchonine to resolve the β-substituted propionic acids that he prepared. The first attempts to resolve β-(α-furyl)-valeric acid with quinine were not very encouraging so a number of other active bases were tested.

Equivalent amounts of strychnine and acid were dissolved in boiling dilute alcohol. The solution was decolorized with carbon and filtered. Spontaneous evaporation of the solvent caused the separation of an oily layer that could not be in-

duced to crystallize by cooling or by dissolving and re-precipitating from the common organic solvents.

Equivalent amounts of cinchonine and acid were dissolved in 95 percent alcohol and the solution allowed to evaporate. The addition of acetone to the concentrated solution caused the separation of a few crystals, m.p. 188-193°. The rest of the salt could not be crystallized. The yield was so low that this method was abandoned.

Acid sufficient to form the salt was added to a boiling alcoholic solution of brucine. The solution was boiled with carbon and filtered. After evaporation to a small volume the residue solidified. The crystals were extremely soluble in all the common organic solvents except ether and hexane. Combinations of solvents did not yield any crystalline products. A boiling ether extract of the above residue deposited white crystals that melted up to 65°. Repeated extraction seemed to separate the crude crystals into a low melting fraction, slightly soluble in ether, and a less soluble higher melting fraction. The solubility of the first fraction was so low, however, that this method of separation was not practical. Neither of these types of crystals induced crystallization of any of the syrups obtained previously. The syrup that precipitated from a dilute alcoholic solution of the salt deposited crystals after standing for several weeks. They could not be completely separated from the non-crystalline material because of their great solubility. Crystals separated mechanically (m.p. 88-95°)

could not be recrystallized any more readily than the original salt.

A number of synthetic bases have been used in the resolution of acids. Betti recommended the use of β-naphthol phenylaminomethane as a resolving agent; therefore, some of this base was prepared (45) and resolved (46) according to his directions. The d-base was readily obtained but preparation of the l-base as a resolving agent was not practical because of the instability of the alcoholic solution of the l-base-d-tartrate. Evaporation of the solution even at very low pressures caused almost complete decomposition of the amine. Equivalent amounts of the d-amine and β-(α-furyl)-valeric acid were dissolved in warm acetone. After standing overnight the solution had deposited crystals, which, after several recrystallizations, melted at 151-153°. When equivalent amounts of the acid and base were dissolved in alcohol, crystals were obtained that, after recrystallization, melted at 160-162°. Boiling either of these compounds with hydrochloric acid produced some of the amine hydrochloride, but they were not affected by warming with alkali. Thus, they were not salts. They were found to be condensation products of the amine with acetone and benzaldehyde respectively. The benzaldehyde arose from decomposition of part of the amine. It was found possible to form a salt by mixing cold ethyl acetate solutions of the amine and acid and allowing the resulting solution to evaporate at room temperature. The salt became discolored and smelled strongly of the free acid

after standing for a few hours. Obviously this base is too weak to form stable salts with this acid.

The active α-phenylethylamines have been used in the resolution of some acids. Some of the amine was prepared and resolved by Ingersoll's (47) directions. Some of the amine, from freshly decomposed l-malate-d-amine, was dissolved in 95 percent alcohol containing an equivalent amount of the acid. Evaporation of some of the solvent caused precipitation of all of the salt present. This melted at 93-96° and was apparently the d-base-dl-acid salt. It was very soluble in most organic solvents, and any combination of solvents that allowed re-crystallization produced the same salt. An attempt was made to resolve the acid with this amine by the equilibrium method of Pope and Peachy (48). Some of the acid was dissolved in dilute alcohol and enough of the amine added to form the salt of one isomer. The rest of the acid was neutralized by the careful addition of ammonia. The oil that separated on slow evaporation of this solution could not be crystallized.

Since these methods failed to resolve the acid, further attempts were made to effect this by means of quinine. In the first tests made with this alkaloid, waxy crystals were deposited from aqueous methyl and ethyl alcohol solutions of the salt. They were very soluble in all organic solvents and could not be purified very easily. When they were used to seed a very cold aqueous acetone solution of the quinine salt, crystallization occurred readily. Forty-four grams of acid

were dissolved in 250 cc. of boiling acetone and 90 grams of quinine added. The solution was diluted with 75 cc. of water, decolorized, and filtered. It was cooled to 10°, and water was added till a faint turbidity persisted. After being seeded, the solution was kept at 10° for two days when nearly 90 per-cent of the total salt had crystallized. This could be readily recrystallized by dissolving in somewhat more dilute acetone, seeding, and cooling in the icebox. After systematic re-crystallization, the purest fraction, 6 grams after six re-crystallizations, melted at 79-86°. Thorough drying raised the melting point to 82-89°.

Analysis

Calculated for $C_{29}H_{36}O_5N_2$: N, 5.68

Found: N, 5.48

The salt was decomposed by warming with dilute hydrochloric acid. The acid was extracted with ether, and the ether solution dried over anhydrous sodium sulphate. Two grams of the acid were obtained (b. p. 132-133°/10mm.) having the rotation, α_D^{25} +10.80°.

The most soluble fraction of the quinine salt was de-composed and 10 grams of acid obtained (b. p. 130-133°/10mm.) for which, α_D^{25} -4.22°. Since cinchonine many times crystallizes out with the isomer that forms the most soluble salt with quinine, the impure l-acid was combined with 17.5 grams of this alkaloid in dilute alcohol. The oil that separated from this solution could not be crystallized. Since the l-acid cannot be

obtained optically pure, there is no way of checking the purity of the d-acid obtained, so the recrystallization of the d-acid quinine salt was not continued any further. Acid recovered from the most soluble quinine salt was used in the dispersion measurements (b.p. 106-110°/2mm.).

Determination of rotatory dispersion

α_D^{27} -3.44°	$[\alpha]_D^{27}$ -3.17°
α_{5780}^{27} -3.57°	$[\alpha]_{5780}^{27}$ -3.29°
α_{5461}^{27} -4.10°	$[\alpha]_{5461}^{27}$ -3.77°
α_{4358}^{27} -7.48°	$[\alpha]_{4358}^{27}$ -6.89°

α_D^{25} -0.20° (benzene, c = 5.75) $[\alpha]_D^{25}$ -3.48°

Dispersion ratio, $\alpha_{4358}/\alpha_{5461} = 1.83$

All measurements were made using a one decimeter micro polariscope tube in the Schmidt and Haensch polariscope reading to .01°. A 110 volt sodium lamp was used for illumination to read the sodium D line. For the mercury lines a capillary, 85 watt, high intensity mercury vapor lamp was used. This was mounted inside a brass protective shield in which a small lens (1 1/4 in. diam.) was held to focus the light into the polariscope.

To isolate the mercury yellow lines (5769A and 5790A), Corning filters numbers 348 and 430 were used. For the green line (5461A), numbers 351, 512, and 430 were used. For the blue line (4358A), a piece of cobalt glass was used. These filters were tested spectroscopically to be sure that in each case all undesirable lines were removed.

Preparation of β-(α-furyl)-caproic acid

The preparation of this was carried out as in the case of β-(α-furyl)-valeric acid. A Grignard reagent was prepared from 6.34 grams (0.26 moles) of magnesium and 32 grams (0.26 moles) of n-propyl bromide. To this reagent was added 57 grams (0.24 moles) of diethyl furfurylidenemalonate. The yield of substituted malonic ester was 53 grams (b.p. 150-153°/8mm.), representing 78.6 percent of the theoretical. Another smaller run resulted in a 75 percent yield.

One hundred and five grams (0.372 moles) of β-(α-furyl)-n-butylmalonic ester were hydrolyzed and decarboxylated. The residue was distilled at reduced pressure and 60.8 grams (90 percent) of β-(α-furyl)-caproic acid obtained, b.p. 148°/11mm; n_D^{25} 1.4740; d_4^{26} 1.059.

Maxim and Zugravescu (44) prepared this acid (b.p. 148°/6mm) by hydrolysis of its diphenylamide.

Resolution of β-(α-furyl)-caproic acid

The strychnine and cinchonine salts of this acid could not be crystallized. The brucine salt crystallized from an acetone solution after evaporation to a very small volume, but it could not be purified from this solvent. It was very soluble in all organic solvents except ether and hexane, and combinations of these solvents yielded only syrups.

The acid was partially resolved by means of quinine.

Forty-three grams of acid were added to 90 grams of quinine in 300 cc. of boiling acetone. The solution was decolorized, diluted with 200 cc. of water, and filtered. It was then cooled to 10° and diluted with water till turbid. After standing for 24 hours, most of the salt had crystallized. It was recrystal - lized from about six parts of 40 percent aqueous acetone by cooling to 20°. It was recrystallized four times more in the same way, m.p. 86-92°.

Analysis

Calculated for $C_{30}H_{38}O_5N_2$: N, 5.54

Found: N, 5.48

A small amount of the salt was decomposed and the acid recovered (b.p. 110-111°/2mm.) for which, α_D^{27} +4.83°. This was probably not optically pure, but since the opposite isomer could not be crystallized to check this, the resolution was not carried any farther. Less pure fractions of the salt were combined (19.9 grams) and the acid freed. Six and one-tenth grams were obtained (b.p. 110-113°/3mm.).

Determination of rotatory dispersion

α_D^{26} +2.69°	$[\alpha]_D^{26}$ +2.54°
α_{5780}^{26} +2.81°	$[\alpha]_{5780}^{26}$ +2.66°
α_{5461}^{26} +3.27°	$[\alpha]_{5461}^{26}$ +3.12°
α_{4358}^{26} +6.09°	$[\alpha]_{4358}^{26}$ +5.75°

α_D^{25} +0.30° (benzene, c = 7.5) $[\alpha]_D^{25}$ +4.00°

Dispersion ratio, $\alpha_{4358}/\alpha_{5461}$ = 1.86

Preparation of β-(α-furyl)-β-phenylpropionic acid

A Grignard reagent was prepared from 5.35 grams (0.22 moles) of magnesium and 34.5 grams (0.22 moles) of brombenzene. Forty-eight grams (0.20 moles) of diethyl furfurylidenemalonate were added as in the preparation of β-(α-furyl)-valeric acid, and the rest of the procedure carried out. The substituted malonic ester was a thick yellow oil (b.p. 193-197°/8mm.). The yield was 26.3 grams, 74.5 percent of the theoretical. Another similiar run gave about the same yield. Maxim and Georgescu (49) prepared the ester in the same way and reported a yield of 77 percent of a product boiling at 203°/14mm.

Fifty-two grams (0.17 moles) of the ester were added to a 35 percent solution of 24 grams (0.43 moles) of potassium hydroxide. A few grams of ethyl alcohol were added, and the mixture refluxed gently for three hours. The dibasic acid was liberated, separated, and decarboxylated. The monobasic acid was not distilled because of excessive decomposition at the high temperature. The residue was dissolved in hot dilute alcohol, decolorized, and crystallized. The pale yellow, fluffy crystals weighed 27.9 grams (78.5 percent) and melted at 101-104°. Maxim and Georgescu reported a melting point of 105°.

Resolution of β-(α-furyl)-β-phenylpropionic acid

Two grams of acid were added to 3.65 grams of brucine in acetone. The syrup that separated on partial evaporation of the solvent could not be crystallized. A preliminary test showed

that the quinine salt crystallized easily. Fifty-seven grams of quinine were dissolved in 125 cc. of hot 95 percent alcohol and 15.5 grams of acid added. The solution was diluted with 25 cc of water and allowed to stand for a few hours. At the end of this time a mass of crystals had been deposited. The salt was easily crystallized from aqueous acetone but still melted over a wide range after a number of recrystallizations. Ethyl acetate seemed to separate the isomers somewhat better, but after several recrystallizations from this solvent, the salt still melted over a wide range. Seventeen grams were recovered, $[\alpha]_D^{27}$ -13.0° (ethanol, c = 5.0).

Three grams of the dl-acid in 30 percent alcohol were treated with one-half the equivalent amount (0.90 grams) of d-α-phenylethylamine, and the excess acid was carefully neutralized with ammonia. Fine, needle-like crystals were deposited while standing overnight (m.p. 163-167°). A small amount of the acid (m.p. 98-100°) freed from the salt had the rotation $[\alpha]_D^{28}$ -13.4° (ethanol).

Nine grams of the l- and dl-acids recovered from the attempted resolution with quinine were dissolved in 75 cc. of 60 percent alcohol, and sufficient d-α-phenylethylamine (2.7 grams) added to react with all of the l-acid. The excess acid was neutralized with ammonia and the salt allowed to crystallize. The melting point of the salt reached a maximum (168-173°) after the third recrystallization, but the rotation of the acid liberated from the salt rose steadily

until after the seventh recrystallization it was α_D^{32} -1.53° (ethanol, c = 3.7), $[\alpha]_D^{32}$ -56.3°. Two more recrystallizations of the salt did not change the rotation of the acid (m.p. 85-87°, from acetic acid). The salt was not very stable and considerable decomposition took place during the recrystal - lizations. The total yield was only 2.7 grams from which 1.7 grams of active acid were recovered.

The quinine and ammonium salts from the above filtrates were decomposed and 7.1 grams of d- and dl-acid recovered. This was combined with 2.65 grams of l-α-phenylethylamine, the amount calculated to react with the d-acid as determined by the rotatory power. The 60 percent alcohol solution of the mixture was neutralized with ammonia, and the salt crystallized. An acid of maximum rotation was obtained from the salt after six recrystallizations. Two grams of salt yielded 1.2 grams of acid, m.p. 85°, after recrystallization from acetic acid.

Analysis

Calculated for $C_{21}H_{28}O_8N$: N, 4.15

Found: N, 3.98

Calculated for $C_{13}H_{12}O_8$: C, 72.20 H,

Found: C, 72.30 H,

Determination of rotatory power

α_D^{25} +0.76° (benzene, c = 0.89) $[\alpha]_D^{25}$ +85.4°

α_D^{25} +0.90° (ethanol, c = 1.3) $[\alpha]_D^{25}$ +69.1°

α_{5780}^{25} +1.07° (ethanol, c = 1.3) $[\alpha]_{5780}^{25}$ +79.6°

α^{25}_{5461} +1.26° (ethanol, c = 1.3) $[\alpha]^{25}_{4358}$ +94.4°

α^{25}_{4358} +2.08° (ethanol, c = 1.3) $[\alpha]^{25}_{4358}$ +160.°

Dispersion ratio, $\alpha_{4358} / \alpha_{5461} = 1.70$

Catalytic Hydrogenation of β-Substituted Propionic Acids

Catalytic hydrogenation of β-(α-furyl)-valeric acid

A number of catalysts have been used for the reduction of the furyl group to the tetrahydrofuryl group. Adkins describes Raney nickel as being a specific catalyst for this reduction. However, he used rather high temperatures for his reductions which would be an undesirable condition for an optically active compound. Palladous oxide as prepared by Shriner and Adams (50) has been used to reduce the furyl group in a number of compounds. A trial run with this catalyst showed absorption of only 80 percent of the calculated amount of hydrogen in 30 hours. Adams (51) platinum oxide catalyst reduces the furyl group readily and also opens the ring, but it is claimed that the first reaction goes quantitatively before any of the second occurs. In a trial run this catalyst caused β-(α-furyl)-valeric acid to take up the required amount of hydrogen in a few hours.

The apparatus used in the hydrogenation consisted of a 25 cc. bulb mounted so that it could be shaken vigorously, and constructed so that neither solvent or catalyst could come in contact with anything but glass. This was connected to a

stationary, graduated reservoir that could be filled with hydrogen saturated with the solvent used.

The acid, 4.35 grams, α_D^{27} -3.44°, was reduced in four portions of approximately one gram each. Ninety-five percent alcohol was used as the solvent, and 40 mg. of fresh catalyst was used for each of the reductions. The required amount of hydrogen was taken up in about five hours. It was still being absorbed steadily when the shaker was stopped. The catalyst was filtered off, and the solvent was distilled at reduced pressure. An equal volume of dry benzene was added to the residue and evaporated at atmospheric pressure to remove any water present. The residue was distilled at reduced pressure, and two main fractions were obtained. The first, 1.3 grams, came over at 97-112°/2mm. It contained considerable non-acidic material, as shown by the neutral equivalent, and was probably the lactone with some unreduced acid. This means that some of the furan ring was opened before all of it was reduced, and the γ-hydroxy acid was decomposed by distillation. The constants were: α_D^{25} -1.56°, n_D^{20} 1.4502, and d_D^{25} 0.998.

The second fraction, 2.1 grams, distilled at 118-124°/2mm., n_D^{20} 1.4651, d_4^{25} 1.063.

Analysis

Calculated for $C_9H_{16}O_3$: N. E., 172

Found: N. E., 174

Determination of rotatory dispersion

α_D^{25} +0.26° $[\alpha]_D^{25}$ +0.24°

α^{25}_{5780} +0.28°	$[\alpha]^{25}_{5780}$ +0.26°
α^{25}_{5461} +0.36°	$[\alpha]^{25}_{5461}$ +0.34°
α^{25}_{4358} +0.79°	$[\alpha]^{25}_{4358}$ +0.74°

Dispersion ratio, $\alpha_{4358}/\alpha_{5461}$ =2.19

Catalytic hydrogenation of β-(α-furyl)-caproic acid

This acid, 4.2 grams α^{25}_{D}+2.69°, was reduced in the same way as β-(α-furyl)-valeric acid. The dried product was fractionated. The first fraction, 1.2 grams, was collected at 99-112°/1mm., and was probably unreduced acid and lactone, n^{20}_{D} 1.4514, d^{25}_{4} 0.981, α^{25}_{D}+2.31°.

The main fraction, 2.1 grams, distilled at 125-130°/2mm., n^{20}_{D} 1.4614, d^{25}_{4} 1.036.

Analysis

Calculated for $C_{10}H_{18}O_3$: N. E., 186.

Found: N. E., 187.

Determination of rotatory dispersion

α^{26}_{D} -0.50°	$[\alpha]^{26}_{D}$ -0.48°
α^{26}_{5780} -0.52°	$[\alpha]^{26}_{5780}$ -0.50°
α^{26}_{5461} -0.59°	$[\alpha]^{26}_{5461}$ -0.57°
α^{26}_{4358} -1.38°	$[\alpha]^{26}_{4358}$ -1.33°

Dispersion ratio, $\alpha_{4358}/\alpha_{5461}$ =2.34

Catalytic hydrogenation of β-(α-furyl)-β-phenylpropionic acid

One and one-half grams of β-(α-furyl)-β-phenylpropionic acid, m.p. 100-102°, $[\alpha]^{28}_{D}$+10.0° (ethanol, c = 1), were shaken with 50 mg. of platinum oxide in 95 percent alcohol until the

calculated amount of hydrogen had been taken up. The reduction of this acid was somewhat slower than the others. The solution was filtered and then concentrated at reduced pressure. The residue was reserved for the reduction with hydrogen iodide.

One and fifteen-hundredths grams of β-(α-furyl)-β-phenylpropionic acid, m.p. 85°, $[\alpha]_D^{25}$ +69.1° (ethanol, c = 1.0), were shaken with 60 mg. of platinum oxide. The hydrogenation was stopped after 12 hours although only 90 percent of the required amount of hydrogen had been taken up. The solution was freed from the catalyst, concentrated, and dried as before. The residue was fractionated at reduced pressure yielding 0.3 grams of a low boiling fraction and 0.35 grams having the boiling point, 158-162°/2mm. The last fraction was a pale yellow syrup which was extremely viscous.

Analysis

Calculated for $C_{13}H_{16}O_3$: N. E., 220.

Found: N. E., 224.

Determination of rotatory dispersion

$[\alpha]_D^{24}$ +35.9° (benzene, c = 3.2)

$[\alpha]_{5780}^{24}$ +37.7° (benzene, c = 3.2)

$[\alpha]_{5461}^{24}$ +44.4° (benzene, c = 3.2)

$[\alpha]_{4358}^{24}$ +78.1° (benzene, c = 3.2)

Dispersion ratio, $\alpha_{4358} / \alpha_{5461}$ =1.76

Reduction of the Tetrahydrofuryl Group to the n-Butyl Group

Reduction of β-(α-tetrahydrofuryl)-valeric acid to β-(n-butyl)-valeric acid

The tetrahydrofuryl group was reduced to the n-butyl group in two steps. The oxygen was first removed by treatment with liquid hydrogen iodide at room temperature, and the iodine was then removed from the resulting compound by shaking with zinc and hydrochloric acid. The hydrogen iodide was generated by dropping hydriodic acid (sp. gr. 1.50) on phosphorus pentoxide. The gas was passed through a drying tube containing more of the oxide and was then condensed in a bath of acetone and solid carbon dioxide.

One and one-tenths grams of β-(α-tetrahydrofuryl)-valeric acid, α_D^{25} +0.26°, were added to two times its volume of liquid hydrogen iodide in a pyrex tube. The tube was sealed and allowed to warm up gradually. Considerable heat was evolved as the liquids mixed. The tube was allowed to stand for three days, cooled, and opened. The excess hydrogen iodide was evaporated off, and the thick liquid, black with iodine, was washed out of the tube with benzene. The solution was washed with water to remove most of the iodine and then shaken with dilute thiosulphate solution to remove the rest. The benzene was evaporated off, and the iodo-acid was shaken vigorously with an excess of 20 mesh zinc and hydrochloric acid for

15 hours. The acid was added very slowly at the first of the reaction so that the mixture never became warm. This was to make sure that there was as little formation of the lactone as possible. The product was extracted, dried, and fractionated. The main part, 0.5 grams, distilled at 140-142°/20mm. α_D^{25} -2.70°. Levene and Marker (52) reported b.p. 132°/12mm. for β-(n-butyl)-propionic acid. The acid obtained contained no iodine, but the neutral equivalent showed the presence of considerable non-acidic material. A dilute alcoholic solution of the acid was carefully neutralized, and enough silver nitrate was added to precipitate the silver salt.

Analysis

Calculated for $C_9H_{17}O_2Ag$: Ag, 42.33.

Found: Ag, 42.06.

The silver salt was decomposed by warming with dilute hydrochloric acid. The acid was extracted, dried, and concentrated.

Determination of rotatory power

α_D^{25} -0.23° (benzene, c = 33.0) $[\alpha]_D^{25}$ -0.70°

The lower boiling fraction obtained from the catalytic reduction of β-(α-furyl)-valeric acid, α_D^{25} -1.56°, was reduced and purified by precipitation of the silver salt (Ag, 41.86 percent). The acid obtained had the rotation, $[\alpha]_D^{24}$ -0.54° (benzene, c = 12).

Reduction of β-(α-tetrahydrofuryl)-caproic acid to β-(n-butyl)- caproic acid

One gram of β-(α-tetrahydrofuryl)-caproic acid, α_D^{25} -0.50°, was treated with liquid hydrogen iodide and then with zinc and hydrochloric acid. The product was purified by precipitation of the silver salt.

Analysis

Calculated for $C_{10}H_{19}O_2Ag$: Ag, 38.65.

Found: Ag, 38.80.

The silver salt was decomposed, and the acid was extracted and concentrated.

Determination of rotatory power

α_D^{25} +0.07° (benzene, c = 25) $[\alpha]_D^{25}$ +0.28°

The lower boiling fraction obtained from the catalytic hydrogenation of β-(α-furyl)-caproic acid was reduced and then purified by precipitation of the silver salt (Ag, 38.95 percent). The acid freed from the salt had the rotation, $[\alpha]_D^{25}$ +1.07° (benzene, c = 31).

Reduction of β-(α-tetrahydrofuryl)-β-phenylpropionic acid to β-(n-butyl)-β-phenylpropionic acid

The β-(α-tetrahydrofuryl)-β-phenylpropionic acid obtained by catalytic hydrogenation of β-(α-furyl)-β-phenylpropionic acid, 1.5 grams, $[\alpha]_D^{25}$ +10.° (ethanol), was treated with

hydrogen iodide and then with zinc and hydrochloric acid. The acid was extracted, dried, and distilled. The first fraction (0.2 grams) distilled over below 120°/1mm. The higher boiling fraction came over at 140°/1mm.; $n_D^{20°}$ 1.5041, d_4^{2} 0.999. Levene and Marker (53) reported, b.p. 165°/4mm., d_4^{25} 0.996 for β-(n-butyl)-phenylpropionic acid.

Analysis

Calculated for $C_{13}H_{18}O_2$: N. E., 206.

Found: N. E., 210.

Determination of rotatory power

α_D^{28} +1.30 (benzene, c = 39.4) $[\alpha]_D^{28}$ +3.30°.

DISCUSSION OF RESULTS

Since none of the parent acids were completely resolved, the magnitude of the rotations between the different series cannot be compared. Such a comparison would be questionable even if optically pure acids had been used because of the evidence of racemization during the course of the experimental work. In every case where an active acid containing the furyl group was distilled the rotation was decreased. There must be racemization also during the reductions because the rotations of β-(n-butyl)-caproic acids reduced by different routes do not agree. There is fair agreement between the rotations of β-(n-butyl)-valeric acids; thus, the degree of racemization must depend on the conditions rather than on the action of any particular reagent.

The data on rotatory power have been summarized in Table 1. The dispersion ratios vary over a wide range. A value of about 1.70 has been found normal for some aliphatic acids, but unsaturated acids may have higher ratios and still exhibit normal rotatory dispersion. Thus, β-(α-furyl)-valeric and -caproic acids with values of 1.83 and 1.86 may have normal dispersions, but those of the corresponding tetrahydrofuryl acids are distinctly complex. All of the acids containing the furyl group are very slightly yellow when freshly prepared. This color is greatly intensified when viewed through the polar-

iscope tube, but the dispersion ratios show that there are no anomalies in their dispersion curves in the range of the spectrum examined.

Levene found that in several homologous series of β-substituted acids the ethyl member rotated in the opposite direction to the propyl. Thus, he and Marker (54) have shown that d-β-(n-butyl)-caproic acid is configurationally related to l-β-(n-butyl)-valeric acid. The acids from which these are derived by reduction are also related. Table 1 shows that the relation observed by Levene also holds in these series; for, in each step the acid containing the ethyl group is opposite in sign to the one having the propyl group. It is surprising to find that the configurationally related acids do not form the least soluble salts with quinine. One would expect that configuration and solubility would be more closely related in compounds so nearly alike in structure. This illustrates the fact that configurational relationships must be accepted with extreme caution except when established by chemical methods under conditions where there is no possibility of inversion. There may be some doubt about comparing the configurations of the ethyl and propyl acids containing the tetrahydrofuryl group, but it is probable that the asymmetric addition of hydrogen would take place in the same way under the influence of the ethyl group as for the propyl group. The sign of the rotation of the first asymmetric carbon in this compound is in doubt since the sign of rotation of the entire

Table 1

Rotatory Power of β-(α-Furyl)-propionic Acids and their Reduction Products

Acids	$[\alpha]_D$[a]	$[\alpha]_D$ (benzene)	$[\alpha]_D$ (ethanol)	Dispersion ratio
β-(α-Furyl)-valeric	-3.17°	-3.48°		1.83[a]
β-(α-Furyl)-caproic	+2.54	+4.00°		1.86[a]
β-(α-Furyl)-β-phenyl-propionic		+85.4°	69.1°	1.70[c]
β-(α-Tetrahydrofuryl)-valeric	+0.24°			2.19
β-(α-Tetrahydrofuryl)-caproic	-0.48°			2.34
β-(α-Tetrahydrofuryl)-β-phenylpropionic		+35.9°		1.76
β-(n-Butyl)-valeric		-0.70°		
β-(n-Butyl)-caproic		+0.28°		
β-(n-Butyl)-β-phenyl-propionic		+23.1°[b]		1.64

[a]Homogeneous

[b]This value has been calculated. It is the rotation that would have been obtained if the acid of maximum rotatory power had been used in the reductions.

[c]Ethanol

molecule may be controlled by that of the second asymmetric carbon. Thus, there can be no comparisons made between the sign of the first carbon in this compound with its sign in the unreduced or completely reduced acids in any of the series studied.

If in a series of active compounds there are three constant radicals and one that is variable, the asymmetry product for the series may be written

$$\alpha = \frac{(a-b)(a-c)(b-c)\ [(a-x)(b-x)(c-x)]}{(a+b+c+x)^n}$$

where a, b, and c represent the group constants of the unaltered radicals, and x represents the group constant of the radical that is varied. This shows that if the rotation is plotted against the group constants it will be zero when x is equal to a, b, or c. Curves showing the change in the sign of rotation with change in x are given in Graph 1 where the group constants are represented by the electron-sharing-abilities of the radicals. No attempt has been made to indicate the magnitude of the rotation, neither have the E. S. A.'s of the radicals been placed according to their relative values but merely in the order determined by the dissociation constants as given in Table 2. The value of H is from the dissociation constant of ammonia; the values for the other radicals are from the dissociation constants of the corresponding acids.

Curve I shows that if the furyl group in 1-β-(α-furyl)-valeric acid is replaced by any group intermediate between CH_3COOH and H in E. S. A. the sign of the rotation should

remain unchanged. Experimentally it was found that the sign of rotation changes when the furyl group is replaced by the tetrahydrofuryl group; but, as has been pointed out the sign of this member of the series is in doubt. In the next

Table 2

Dissociation Constants Showing the Order of the Electron-Sharing-Abilities of the Radicals in Graph 1

Radicals	$K(H_2O)$
CH_2COOH	1.6×10^{-3}
C_4H_3O	7.6×10^{-4}
C_4H_7O	1.4×10^{-4}
C_6H_5	7.0×10^{-5}
H	1.75×10^{-5}
C_4H	1.56×10^{-5}
C_3H_7	1.50×10^{-5}
C_2H_5	1.32×10^{-5}

step, however, there is no doubt about the sign or the configuration. There is only one asymmetric carbon and the configuration must be the same as the original acid. According to the theory any group replacing the furyl group having an E. S. A. intermediate between C_2H_5 and H should have a positive rotation whereas the opposite was found experimentally. The acid containing the n-butyl was negative.

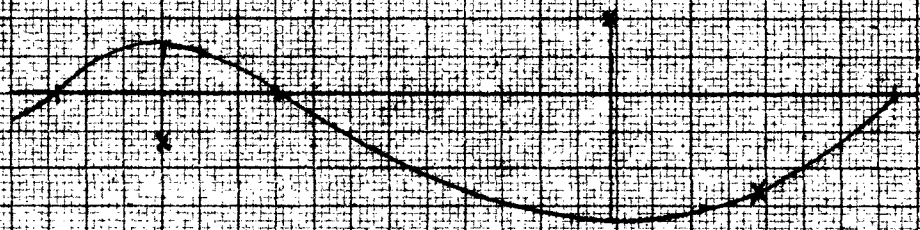
Curve II shows the effect of varying the furyl group in d-β-(αfuryl)-caproic acid. The experimental results exactly

Form E-3

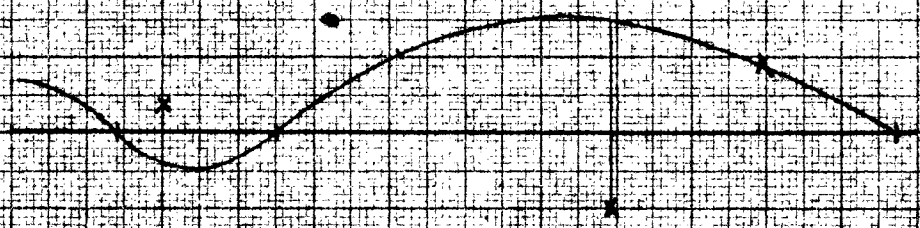
Graph No 1

Comparison of Rotation with "Asymmetry Product"

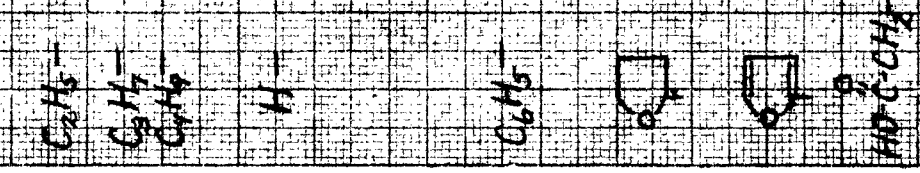
Curve I. β-(α-Furyl)-valeric acid



Curve II. β-(α-Furyl)-caproic acid



Curve III. β-(α-Furyl)-β-phenylpropionic acid



parallel those obtained with β-(α-furyl)-valeric acid. The sign of rotation of each of the reduced acids is opposite to what would be expected from the proposed theory.

The course of changes in rotatory power to be expected by varying the furyl group in d-β-(α-furyl)-β-phenylpropionic acid has been shown in Curve III. This shows that the corresponding acids having the furyl, tetrahydrofuryl, and n-butyl groups should have the same sign. This is what was found experimentally. The fact that reduction of the furyl group to the tetrahydrofuryl group does not change the sign as in the aliphatic acids may be because the phenyl group gives the first asymmetric carbon a high enough rotation so that it controls the rotation of the molecule.

Assuming that the product-of-asymmetry theory is valid, there are two possible explanations of its failure to predict the signs of the rotations of β-(n-butyl)-valeric and -caproic acids. Since dissociation constants do not always place the lower alkyl groups in the same order, it may be that the values used here do not express the effect of these groups on the rotatory power. This does not seem likely since Levene has shown that the effect of the n-alkyl groups vary with their molecular weights which is the order used in this study. The other explanation is that hydrogen is out of place. If the E. S. A.'s of the radicals in Graph 1 are in the proper order, it can only be concluded that the product-of-asymmetry theory does not hold or that the E. S. A. of a group does not express

its effect on the rotatory power.

SUMMARY

1. β-(α-Furyl)-valeric acid has been prepared and partially resolved.

2. β-(α-Furyl)-caproic acid has been prepared and partially resolved.

3. β-(α-Furyl)-β-phenylpropionic acid has been prepared and partially resolved.

4. The furyl group of the β-substituted propionic acids has been reduced stepwise to the n-butyl group.

5. Reduction of the furyl group in β-substituted propionic acids has been shown to cause some racemization.

6. Catalytic hydrogenation of the furyl group in β-substituted propionic acids in the presence of platinum oxide has been shown to cause some opening of the furan ring before it is completely hydrogenated.

7. The effect of reduction on the rotatory power of β-(α-furyl)-β-phenylpropionic acid indicates that the product-of-asymmetry can be applied when the E.S.A.'s of radicals are used as group constants.

CONCLUSIONS

1. The β-(α-furyl)-propionic acids are too difficult to resolve and too easily racemized to be used for conclusive studies on the effect of reduction of the furyl group on rotatory power.

2. The contradictory results obtained may be explained by the use of different radicals in further studies.

3. Some method should be devised for determining the effect of the hydrogen atom on the rotatory power of a compound.

4. The negative results obtained may be due to the fact that the E. S. A. of an alkyl group is not measured by the dissociation constants of its acid or amine.

5. No conclusions can be drawn from the data obtained concerning a definite relationship between the E. S. A.'s of radicals, the product-of-asymmetry theory, and rotatory power.

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